REMARKS

Reconsideration is requested.

Claims 76-106,109 and 111-114 are pending. Claims 76-105 and 112-114 have been withdrawn from consideration.

Claim 106 has been revised, without prejudice, to correct the inadvertent additional zero in the identification of the sequence of the claim. No new matter has been added. The amendment obviates the Section 112, second paragraph, rejection of claim 106. The amendment of claim 111 obviates the Section 112, second paragraph, rejection of claim 111. The Section 112, second paragraph, rejection of claims 106, 109 and 111 is obviated by the above amendments and withdrawal of the rejection is requested.

The Section 112, first paragraph "enablement", rejection of claims 106, 109 and 111 is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following comments.

The Examiner's criticism of the applicants previous reliance on Wong et al (2007) PNAS 104 19040-19045 because the in vitro results "do not predictably extrapolate to *in* vivo anti-cancer activity" (see page 7 of the Office Action dated March 6, 2009) is not understood as the present claims define "methods of identifying a compound as a putative anti-cancer agent" and not to specific compounds whose anticancer activity is predicted only from *in vitro* studies.

One of ordinary skill in the art will appreciate that *in vitro* experiments are a useful tool to identify compounds as potential therapeutic agents. The fact that the *in*

vitro experiments may not directly extrapolate to *in* vivo therapeutic activity does not demonstrate that the *in vitro* methods would require undue experimentation.

In vitro assays are widely used throughout the pharmaceutical industry for early stage drug development (see figure 1 of Zips et al (in vivo 19: 1-8 (2005)); of record) and are an important tool in identifying promising compounds for further study. Zip for example, states on page 3, left column, first paragraph:

> Compared to animal tumor models, *in vitro* methods are less expensive and less time consuming, thereby allowing evaluation of large quantities of new anticancer agents. Molecular methods to prove and quantify the potential of several drugs to affect the molecular target…facilitate the selection of promising candidate drugs.

In vitro assays are therefore used to identity compounds as possessing putative activity. These compounds are then extensively tested in subsequent stages of drug development, including in animal models, to assess whether they possess activity *in vivo*. Compounds which are found to be active *in vivo* may then be tested in the clinic.

In other words, despite the fact that *in vitro* activity may not necessarily extrapolate to *in vivo* anti-cancer activity, *in vitro* assays are still an essential part of drug development in identifying initial hits which are worthy of further investigation and can be performed without requiring undue experimentation. The important role of *in vitro* methods in the early stages of drug discovery is confirmed on page 6, left column "Conclusion" of Zips et al, which states;

> A step-wise procedure from *in vitro* to *in vivo* seems reasonable to reduce the large quantity of potential drugs to a few promising agents for further clinical testing.

It is apparent, for example from Zips et al, that, despite their potential pitfalls and limitation, *in vitro* methods play an important role in drug testing (see page 3, left column). The fact that not all compounds identified in an *in vitro* assay will successfully progress through clinical trials does not make the *in vitro* assay any less useful in identifying putative promising drugs for further testing, nor does it support a conclusion that undue experimentation would be required to practice such methods.

For completeness, the applicants note that the specification includes clinical data which demonstrates that there is a very high frequency of mutations in plexinB1 in prostate and breast cancer cells from patients. Cancer genesis and progression is driven by genetic changes, and these plexinB1 mutations are one of the most frequent genetic changes yet found in any form of cancer.

The *in vitro* experimental data, for example in Wong et al, confirms that the identified *in vivo* mutations alter the function of cells *in vitro*.

The combination of *in vivo* and *in vitro* data provides clear clinical evidence that the claimed plexinB1 mutations play a role in the etiology of cancer *in vivo*. This evidence was accepted by the Proceedings of the National Academy of Sciences USA during the peer-review process (see Wong et al).

The totality of evidence of record therefore demonstrates that one of ordinary skill could practice the claimed invention without requiring undue experimentation.

Reconsideration and withdrawal of the Section 112, first paragraph “enablement”, rejection are requested.

The Section 112, first paragraph "written description", rejection of claims 106, 109 and 111, is obviated by the above amendments. Withdrawal of the rejection is requested.

The Examiner's comments spanning pages 11-12 of the Office Action dated March 6, 2009 regarding the priority application are noted. The above claims are submitted to be supported by the priority application. Genbank version number AB007867.1 is described on page 5, lines 29 and 31 of the priority application no. GB0227908.1. Furthermore, the Genbank accession number "AB007867" is recited in GB0227908.1 at page 3 line 22, page 5 line 6 and page 8 lines 23 and 25. Since only one sequence version (AB007867.1 GI:2662094) is deposited in Genbank under this accession number, the use of the accession number "AB007867" is a clear and unambiguous disclosure of the sequence of AB007867.1. Appendix 1 of the Office Action dated March 6, 2009 evidences that the sequence of SEQ ID NO: 112 is identical to the sequence of AB007867.1. Benefit of the filing date of the claimed priority application should be accorded to present claims.

The Section 132(a) new matter objection to the amendments to the specification filed December 24, 2008 is traversed. The Appendix 1 to the Office Action dated March 6, 2009, provided by the Examiner demonstrates that the sequences referred to in the objected-to amendments to the specification are the same as the sequence referred to in the originally-filed specification. The Appendix 1 provided by the Examiner demonstrates that the SEQ ID NO:112 referred to in the objected-to amendments to the specification was well known to those of ordinary skill in the art. The applicants

disclosure therefore the objected-to sequences in the originally-filed specification and withdrawal of the new matter objection is requested.

The objection to claim 111 stated on page 12 of the Office Action dated March 6, 2009 is obviated by the above amendments. Withdrawal of the objection is requested.

The Section 112, first paragraph "written description", rejection stated on pages 12-16 of the Office Action dated March 6, 2009 is believed to be obviated by the above amendments. Claim 106 recite that the plexinB1 nucleic acid comprises the plexinB1 coding sequence of AB007867.1 (SEQ ID NO: 112) with mutations at one or more of the listed sites. Claims 106 and dependent claims 109 and 111 define mutants of the plexinB1 sequence AB007867.1 (SEQ ID NO: 112) and do not encompass nucleic acid sequences which are not related to the sequence of AB007867.1 (SEQ ID NO: 112), as asserted by the Examiner as a basis for rejecting the unamended claims.

Withdrawal of the Section 112, first paragraph "written description", rejection is requested.

The Section 102 rejection of claims 106, 109 and 111 over Venter (WO 02/068579), is traversed. Reconsideration and withdrawal of the rejection are requested in view of the above and the following.

Claim 106 recites that the plexinB1 nucleic acid comprises the plexinB1 coding sequence of AB007867.1 (SEQ ID NO: 112) with mutations at one or more of seventeen listed mutation sites.

Appendix 2 of the Office Action dated March 6, 2009demonstrates that SEQ ID NO: 14076 of WO02/068579 and SEQ ID NO: 112 share only 12.8% sequence identity.

SEQ ID NO: 14076 of WO02/068579 does not correspond to SEQ ID NO: 112 with mutations at one or more of seventeen specific sites recited in the claims. The cited art is not believed to provide each and every aspect of the claimed invention.

WO02/068579 does not disclose a plexinB1 nucleic acid as presently claimed and claims 106, 109 and 111 are not anticipated by WO02/068579. Withdrawal of the Section 102 rejection is requested.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested. The Examiner is requested to contact the undersigned, preferably by telephone, in the event anything further is required in this regard.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: /B. J. Sadoff/
B. J. Sadoff
Reg. No. 36,663

BJS:
901 North Glebe Road, 11th Floor
Arlington, VA 22203-1808
Telephone: (703) 816-4000
Facsimile: (703) 816-4100